REMARKS

Claims 1-9 and 12-20 are pending in this application. Claims 10 and 11 were previously cancelled without prejudice or disclaimer to the subject matter recited therein. Claim 12 has been amended. Claim 19 has been withdrawn as being directed. Claim 20 has been newly added.

Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 12 has been amended to recite "[a] method of producing a room-temperature stable injectable aqueous solution, comprising: dissolving Carprofen or a physiologically acceptable salt thereof and a poloxamer in water to obtain an injectable solution comprising from 0.25 to 30% (w/v) of Carprofen (6-chloro-x-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 0.5% to 20% (w/v) of poloxamer." Support for the amendment to claim 12 can be found throughout the specification and claims as originally filed.

New claim 20 is directed to the "injectable aqueous solution according to claim 1, wherein the injectable aqueous solution is free from precipitate." Support for new claim 20 can be found throughout the specification and claims as originally filed." For example, please *see* the specification at page 2, lines 26-29.

No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, the claims 1-9 and 12-18 have been rejected under 35 USC § 103 (a) as being obvious over Ruchatz et al. in EP 09 55063 ("Ruchatz") in view of Erni et al. in CH 663788 ("Erni") by Chi et al. in US 5,527,832 ("Chi").

The Examiner asserts that it would have been obvious to substitute ibuprofen in the injectable compositions described by Ruchatz with carprofen as described by Erni, especially in view of Chi.

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U. S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because

inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a reasonable expectation of success. In addition, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

It is submitted that a proper case of *prima facie* obviousness has not been established because there is no motivation to modify Ruchatz with either Erni or

Chi to achieve the presently claimed subject matter because doing so would render Ruchatz inoperable for its intended purpose.

Claims 1-9 and 12-18 are, in general, directed to an injectable solution comprising Carprofen or a physiologically thereof, a poloxamer, and water q.s. for injection, and methods of preparing the same.

In contrast to the presently claimed subject matter, Ruchatz describe the an injectable composition containing a combination of two polyoxyethylene-polyoxypropylene copolymers of different molecular weight and an active ingredient. *See* Ruchatz, generally. However, in all of the embodiments exlempified in Ruchatz the formulations comprise a combination of two polyoxyethylene-polyoxypropylene copolymers present in a total amount of greater than 20%, by weight. *See* Ruchatz at examples 1-16, described in tables 1-3. In addition, Applicants note that the only two examples directed to formulations comprising Ibuprofen, i.e., Examples 15 and 16, each contain two polyoxyethylene-polyoxypropylene copolymers in a total amount of 27.5%, by weight of the composition. *See* Ruchatz at examples 15 and 16, described in table 3.

In addition, Erni only describes salts of carprofen having higher bioavailability than carprofen. *See* Erni at the abstract. Chi describes transdermal gel formulations with anti-inflammatory and analgesic activity. However, Applicants note that neither Erni nor Chi are directed to aqueous injectable solutions at all. In contrast, Erni is directed to gels and Chi is directed to compounds in general.

Applicants respectfully submit that there is no motivation to modify Ruchatz with carprofen or salts thereof (as described in Erni or Chi) because doing so would render the formulations described in Ruchatz inoperable for their intended purposes. In particular, contrary to the Examiner's assertion, it is submitted that suggested modification, i.e., substituting carprofen for ibuprofen, would render the formulations described by Ruchatz unsatisfactory for its intended purpose. In this regard, it is submitted that merely substituting ibuprofen with carprofen in the formulations exemplified by Ruchatz, renders the formulations unsatisfactory for injection.

As evidence of the aforementioned, submits herewith the declaration of Dr. Manish Umrethia (hereinafter "the declaration") along with Annex A and Annex B, which are photographs of formulations discussed in the decaration. As described in paragraphs 6-10 and the declaration, Dr Umrethia concludes that the mere substitution of ibuprofen with carprofen leads to an unstable fromulation, which suffers from several deficiencies, thus rendering the formulations insufficient as injectable solutions.

In the declaration, Dr. Umrethia describes the preparation of two formulations according to the description provided in Ruchatz, except that ibuprofen was substituted with carprofen. As discussed at paragraphs 8 and 9, one formulation was a very thick whitish brown paste at room temperature with excessive foaming, which would make this formulation unsuitable for administration by injection. The other formulation resulted in a very foamy, thick gel like formulation, from which air bubbles very difficult to dissipate. Then

referring to Annexes A and B, Dr. Umrethia concludes that both formulations are not suitable for injection as the formulations have poor syringability, non-dissolved carprofen, foamy bubbles, etc.

Applicants respectfully submit that the declaration and Annexes A and B provide ample evidence to rebut the Examiners assertion that it would have been obvious to modify the formulations exlempified in Ruchatz with carprofen. Since there is no motivation to modify the formulations of Ruchatz, Applicants submit that a *prima facie* case of obviousness cannot be established.

In further support of the patentability of the present claims, Applicants respectfully submit that none of the presently cited references teach or suggest carprofen or salts thereof in aqueous injectable solutions. Further, Applicants submit that the mere classification of a chemical compound as a class of drug, e.g., an NSAID, is not enough to suggest that two compounds described in the same class, i.e., carprofen and ibuprofen, have similar pharmacokinetic or pharmaceutical properties. Therefore, the understanding that carprofen is an NSAID would not be enough to motivate a skilled artisan to substitute carprofen in favor of other known NSAIDS in various formulations with a reasonable expectation of success. As evidenced by the above discussion, this is even more apparent with particular regard to formulating an aqueous injectable solution.

In view of the remarks set forth herein, it is submitted that nothing in any of the applied references, taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

II. New Claim 20

New claim 20 is directed to the injectable aqueous solution according to claim 1, wherein the injectable aqueous solution is free from precipitate.

Applicants respectfully submit that new claim 20 is both novel and non-obvious. Accordingly, Applicants respectfully request an indication that all of the pending claims are now allowable.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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